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BENJAMIN AARON ADLER
MCGREGOR & ADLER
8011 CANDLE LANE
HOUSTON TX 77071

EXAMINER WANG, A	
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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 13

Application Number: 09/238,972
Filing Date: January 27, 1999
Appellant(s): MacLeod, Carol L.

Benjamin Aaron Adler
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed January 28, 2000.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The brief does not contain a statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief. Therefore, it is presumed that there are none. The Board, however, may exercise its discretion to require an explicit statement as to the existence of any related appeals and interferences.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The appellant's statement in the brief that certain claims do not stand or fall together is not agreed with because the methods of claims 1, 2, and 4-9 and the composition of claim 3 would be obvious over the antisense oligonucleotides of claims 16 and 17. Moreover, the claimed methods and compositions cannot be practiced with materially different compounds since the subject matter requires the antisense oligos of claims 16 and 17.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

5,312,733	MACLEOD	5-1994
5,585,479	HOKE et al.	12-1996

Gewirtz et al. "Facilitating oligonucleotide delivery: Helping antisense deliver on its promise." Proc. Natl. Acad. Sci., vol. 93 (April 1996), pp. 3161-3163.

Rojanasakul. "Antisense oligonucleotide therapeutics: drug delivery and targeting." Advanced Drug Delivery Reviews, vol. 18 (1996), pp. 115-131.

Branch. "A good antisense molecule is hard to find." TIBS, vol. 23 (February 1998), pp. 45-50.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 3, 16, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,312,733 (MacLeod).

The invention of the above claims is drawn to any antisense oligo which inhibits CAT2 translation and also to an antisense oligo having SEQ ID NO:2.

MacLeod discloses the CAT2 cDNA double stranded sequence identified as SEQ ID NO: 5, which embraces SEQ ID NO: 2, and also discloses that antisense sequences can be used to inhibit CAT2 translation (paragraph bridging columns 3-4).

Therefore, the invention of the above claims have been anticipated by MacLeod.

2. Claims 3 and 16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention of the above claims is drawn to any antisense oligo which inhibits CAT2 translation and pharmaceutical compositions comprising said antisense oligo.

The specification describes the inhibitory activity of an antisense oligo consisting of SEQ ID NO: 2 and shows that administration of said oligo to Xenopus oocytes comprising polyA+ CAT2 mRNA resulted in restoring L-arginine transport to normal levels as compared to a control oligo (SEQ ID NO: 1).

No other antisense oligos targeted to any other regions of the CAT2 RNA that exhibited inhibitory activity are disclosed nor does the specification provide adequate description of a pharmaceutical composition comprising an antisense oligo targeted to CAT2 RNA.

Thus, the specification as filed fails to provide sufficient written description for any antisense oligo targeted to CAT2 RNA other than SEQ ID NO: 2. It should be noted that the

searched prior art appears to be free of the claimed antisense oligo and therefore provides little guidance, in addition to the specification, that would allow the skilled artisan to find, obtain, or envision any other antisense oligo that is capable of inhibiting CAT2 RNA thereby disrupting translation of cationic amino acid transport protein since the inhibitory activity of any antisense oligo cannot be determined based solely on its primary structure. Moreover, the specification provides no description or guidance as to any pharmaceutical compositions comprising the antisense oligo since no evidence is provided demonstrating the ameliorative effects of treatment with said antisense oligo.

Without such guidance and in view of what was known in the art, the disclosure is not sufficient to describe the claimed genus of antisense oligos targeted to CAT2 RNA and pharmaceutical compositions comprising said oligos.

3. Claims 1-9 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification is only enabling for claims limited to an antisense oligo consisting of SEQ ID NO:2 and a method of inhibiting CAT2 expression using said antisense oligo. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claimed invention is drawn to any antisense oligo targeted to CAT2 mRNA and methods of treatment for diseases involving nitric oxide including sepsis, neoplastic disease, autoimmune disease, cachexia, cerebral malaria, cardiovascular disease, cerebrovascular disease,

capillary leak syndrome, systemic lupus, erythematosus, rheumatoid arthritis, multiple sclerosis, breast cancer, and lung cancer.

The specification teaches the inhibitory activity of an antisense oligo consisting of SEQ ID NO: 2 and shows that administration of said oligo to Xenopus oocytes comprising polyA+ CAT2 mRNA resulted in restoring L-arginine transport to normal levels as compared to a control oligo (SEQ ID NO: 1). Moreover the specification teaches that CAT2 is involved in arginine transport which was shown to be essential in nitric oxide synthesis. In addition, iNOS expression was shown to be correlative with mammary tumorigenesis since mice with a functional iNOS gene developed mammary tumors more rapidly than iNOS knockout mice. The specification does not provide any guidance regarding the administration of any type antisense oligo targeted to CAT2 that would result in an ameliorative effect of any particular pathological state nor does the specification provide sufficient guidance that would enable a skilled artisan to treat a pathological condition by inhibiting CAT2.

The specification gives no guidance to enable a skilled artisan to use an antisense oligo in a method of treating any disease by administering said antisense oligos since the instant specification does not provide any guidance for an antisense oligo that would prove to be effective in the treatment of a pathological condition. Although the specification provides guidance on a singular antisense oligo (SEQ ID NO: 2), it is well known by those skilled in the art that identification of target sites in a given mRNA at which antisense oligos bind to cause inhibition of translation is an unpredictable art. The skilled artisan would recognize that careful screening of oligos targeted to

different sites on a given mRNA to find oligo binding sites for inhibition of translation, may fail to identify such sites in the 5' untranslated region, the coding region, or in the 3' untranslated region of the mRNA and that an oligo binding site that is located only a few bases to either side of an unsuccessful target site may give very effective inhibition of translation (Hoke *et al.*, column 9 and Table 1). In a recently published review of the potential use of antisense oligos as therapeutic agents, Gewirtz *et al.* teach that the inhibitory activity of an oligo depends unpredictably on both the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target (page 3161, second and third columns). This point is further expounded by Branch, who states that "internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules" (page 45, third column).

The clinical application of antisense is also questioned since there are several obstacles that must be overcome such as degradation, molecular size and charge, bioavailability, toxicity, etc... as evidenced by Rojanasakul (abstract) who gives evidence that the use of antisense oligonucleotides in vivo caused renal failure due to toxicity of the antisense oligonucleotide which could be due to nonspecific effects of the oligo itself (page 118, second column, first paragraph). Branch further elucidates this point by stating that "the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curves and therapeutic index is available" (page 46, second column). Additionally, in a recently published review of the potential use of antisense oligos as therapeutic agents, Gewirtz *et*

al. teach that the inhibitory activity of an oligo depends unpredictably on both the sequence and structure of the nucleic acid target site and the ability of the oligo to reach its target (page 3161, second and third columns). Gewirtz *et al.* and Branch conclude by observing that, "the antisense approach has generated controversy with regard to mechanism of action, reliability, and ultimate therapeutic utility" and "that efforts should be increased...to learn how they may be used successfully in the clinic" (page 3162, middle column, last paragraph) and "non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs, these effects must be explored on a case-by-case basis." (page 50), respectively.

Therefore, as discussed above in detail, a skilled artisan would have had to engage in undue trial and error experimentation to resolve that difficulties, as discussed above, to have had practiced the invention as claimed.

(11) Response to Argument

Appellants argue that claims 3, 16, and 17 should not be rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,312,733 since the current application is a continuation in part of 08/187,634, now U.S. Patent No. 5,866,123, which is a continuation in part of 07/686,322, now U.S. Patent No. 5,312,733 which is a continuation in part of 07/509,684, now abandoned. Appellants allege that since 08/187,634 cross references 07/686,322 in the first line of the specification, the current application is entitled to priority benefit of 07/686,322, now U.S. Patent No. 5,312,733. This is not found persuasive since merely cross referencing an application is not synonymous with incorporating by

reference. As noted in the previous Office actions and repeated herein, appellants have not properly incorporated by reference the contents of the previous applications cited above to receive priority benefit of 07/686,322, now U.S. Patent No. 5,312,733.

Appellants also cite Section 201.11 of the MPEP to lend support for priority benefit but as can be clearly seen in the noted section repeated herein "..in either case the second application is entitled to the benefit of the first as to the common subject matter" (emphasis added), appellants are not entitled to said benefit since there was no common subject matter, particularly antisense oligos in application 08/187,634, as noted by appellants, thereby barring applicants from priority benefit to 07/686,322 which was not copending with the current application.

Appellants argue that claims 3 and 16 should not have been rejected under 35 U.S.C. 112, first paragraph, since the specification enables the formation of other inhibitory antisense oligonucleotides by the disclosure of the entire open reading frame (ORF) of CAT2 in the parent application 08/187,634.

As noted in the Advisory action mailed October 19, 1999, and repeated herein, the rejection of record is a written description rejection, not an enablement rejection as argued by appellants, therefore, only arguments pertaining to the rejection of record will be addressed. Appellants allege that the disclosure of the ORF of CAT2 is sufficient to describe an antisense oligonucleotides which inhibit CAT2 expression. This is not found persuasive since appellants

only describe the murine CAT2 transcript without describing any other CAT2 nucleotide transcripts isolated from any other organisms. Without such a disclosure, the skilled artisan would not have been able to envision any antisense oligonucleotide that would inhibit a CAT2 transcript from any organism other than the murine transcript since no description, such as nucleotide sequence, is provided that allow a skilled artisan make, find, or envision said antisense oligonucleotides. Moreover, since the skilled artisan would not be able to envision the claimed antisense oligonucleotides, said artisan could not possibly make a pharmaceutical composition comprising said antisense oligonucleotide.

Appellants argue that claims 1-9 and 16 should not have been rejected under 35 U.S.C. 112, first paragraph, scope of enablement, since appellants have provided adequate guidance that would enable the skilled artisan to find and make antisense oligonucleotides targeted to any CAT2 mRNA as well as methods of treatment using said oligonucleotides.

Appellants allege that the specification as filed provides adequate guidance for a skilled artisan to make antisense oligonucleotides targeted to any CAT2 mRNA and that the cited Hoke et al. patent shows a 55% success rate in finding inhibitory oligonucleotides. Although applicants are accurate in citing Hoke's rate of success, said patent would not be indicative of the success in the claimed invention since Gewirtz et al. and Branch, not addressed by appellants, each disclose the unpredictability of antisense oligonucleotide therapy and inhibition such as appropriate target sites and oligonucleotide accessibility to its target site due

to internal RNA structures. Additionally, as noted above in the written description rejection, appellants have not provided any other CAT2 mRNA sequences that would enable the skilled artisan to make any other antisense oligonucleotide other than SEQ ID NO: 2 without undue trial and error experimentation since the skilled artisan would have to first isolate RNA transcripts from other organisms to make an antisense oligonucleotide that would prove to be inhibitory.

Lastly, appellants allege that the claimed therapies are also enabled since the specification provides evidence that SEQ ID NO: 2 inhibits murine CAT2 RNA *in vitro* and that said inhibition was sufficient to restore normal arginine transport levels thereby affecting nitric oxide production. Although, it is not disputed that arginine transport is related to nitric oxide synthesis, appellants do not provide any evidence or substantive arguments that the administration of antisense oligonucleotides would in fact provide any ameliorative effect on any disease condition. Appellants only allege that "[a]s delivery methods improve, so will the efficiency of antisense therapy", which supports the unpredictability of antisense therapy at the time the invention was made since applicants contend that delivery methods have not yet been refined for efficient antisense therapy at the time of the invention.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

George C. Elliott, Ph.D.
Supervisory Patent Examiner
Technology Center 1600

Andrew Wang
February 14, 2000

McGregor & Adler
8011 Candle Lane
Houston, TX 77071

ROBERT J. HILL, JR.
SUPERVISORY PATENT EXAMINER